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use of the terms strong and weak opioids is not appropriate in the setting of acute postoperative pain management, and that as perioperative physicians, we should avoid the use of these terms. More importantly, we need to acknowledge that all opioids have the potential for causing subsequent opioid dependence.

In addition to the harm to the individual patient caused by subsequent opioid dependence, it is becoming increasingly recognised that poor opioid stewardship also leads to opioid diversion and subsequent opioid dependence in the community.⁹ Currently, there are scant recommendations for safe opioid disposal once patients are discharged from hospital in the UK. Further social harm from opioid use/misuse arises from Drug Driving. In 2015, Drug Driving finally became a criminal offence in the UK; however, it has been argued that the UK legislation is too lenient. In line with Australian guidance, UK patients should be advised not to drive within 4 weeks of opioid dose adjustment.¹⁰

In summary we agree with the thrust of the review article and that further evidence is urgently required to guide opioid deprescribing strategies. In the meantime, in addition to the strategies presented by Soffin and colleagues,¹ we advocate:

- Postoperative opioid administration should be guided by functional activity scores, and not by the NPS
- Opioids prescribed to opioid naïve surgical patients should explicitly not become repeat prescriptions.
- The duration of the opioid prescription needs to be realistic and generally less than 5 days.
- Sustained/modified-release opioid preparations (including transdermal) should be avoided in the management of acute pain.
- Patients need to be given explicit advice on why and how to dispose of excess medication, and be informed how to taper/wean their postoperative analgesia.
- Patients need to be warned about the dangers of drug driving.

Declaration of interest

The authors declare that they have no conflicts of interest.

References

1. Soffin EM, Lee BH, Kumar KK, Wu CL. The prescription opioid crisis: role of the anaesthesiologist in reducing opioid use and misuse. *Br J Anaesth* 2019; **122**: e198–208
2. Brummett CM, Waljee JF, Goesling J, et al. New persistent opioid use after minor and major surgical procedures in US adults. *JAMA Surg* 2017; **152**: e170504
3. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naïve patients and association with overdose and misuse: retrospective cohort study. *BMJ* 2018; **360**: j5790
4. Shah A, Hayes CJ, Martin BC. Characteristics of initial prescription episodes and likelihood of long-term opioid use-United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* 2017; **66**: 265–9
5. Cozowicz C, Poeran J, Zubizarreta N, et al. Non-opioid analgesic modes of pain management are associated with reduced postoperative complications and resource utilisation: a retrospective study of obstructive sleep apnoea patients undergoing elective joint arthroplasty. *Br J Anaesth* 2019; **122**: 131–40
6. Levy N, Sturgess J, Mills P. “Pain as the fifth vital sign” and dependence on the “numerical pain scale” is being abandoned in the US: why? *Br J Anaesth* 2018; **120**: 435–8
7. Levy N, Mills P. Controlled-release opioids cause harm and should be avoided in the management of post-operative pain in opioid naïve patients. *Br J Anaesth* 2019; **122**: e86–90
8. Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. *Br J Anaesth* 2018; **120**: 1335–44
9. Kharasch ED, Brunt LM. Perioperative opioids and public health. *Anesthesiology* 2016; **124**: 960–5
10. Macintyre PE, Huxtable CA, Flint SL, Dobbin MD. Costs and consequences: a review of discharge opioid prescribing for ongoing management of acute pain. *Anaesth Intensive Care* 2014; **42**: 558–74

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The opioid agonist remifentanil increases subjective pleasure

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Editor—The endogenous opioid system is involved in modulation of both pain and pleasure.¹ The opioid system also contributes to mood regulation. In short-term use, exogenous opioids have been suggested to increase positive mood and

reduce negative feelings such as fear and anger.^{2,3} The effects of opioids on emotional responses to external stimuli are not fully understood. Opioids have been shown to reduce perception of anger but leave perception of happiness in facial

expressions unaffected,⁴ or to have no effects on responses to emotional stimuli.⁵ We examined the effects of remifentanyl and naloxone on subjective emotional responses evoked by pleasant and unpleasant film clips. Our hypothesis was that opioid administration either dampens the emotional responses in general, or shifts them towards pleasure, whereas opioid antagonism diminishes the perceived valence of the stimuli.

Male volunteers aged 20–35 yr ($n=31$) completed a set of subjective emotional rating questionnaires and then received three i.v. infusions in the same order: remifentanyl, placebo, and naloxone. The participants were blinded to the sequence

of the infusions. Remifentanyl was administered at an effect-site concentration of 1 ng ml^{-1} using a target-controlled infusion pump. The dose was chosen from a previous study that showed an analgesic effect of this dose without excessive sedation or desaturation.⁶ Naloxone was administered as a $5 \mu\text{g kg}^{-1}$ i.v. bolus over 2 min followed by an infusion at $40 \mu\text{g kg}^{-1} \text{ h}^{-1}$, providing an estimated naloxone plasma concentration of 10 ng ml^{-1} .⁷ A saline bolus identical in volume to the naloxone bolus was administered during the 2 min preceding the remifentanyl and saline infusions. Each infusion lasted 23 min and was followed by a 10-min washout period.

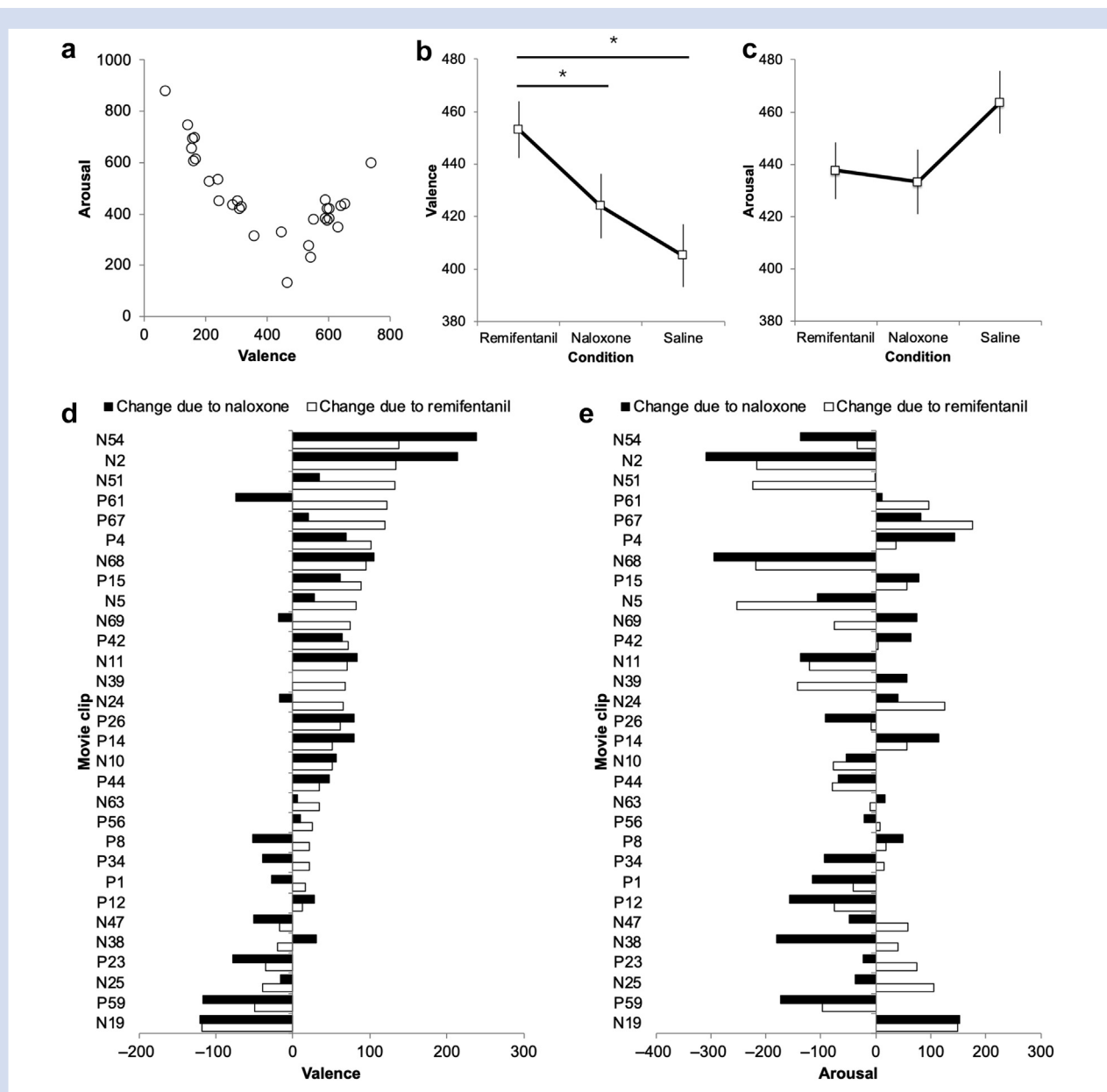


Fig 1. (a) Association between the mean valence and arousal ratings (scale: 0–1000) for each film clip during the saline condition. Means and standard errors of mean for (b) self-reported valence and (c) arousal. Asterisks show significant differences in contrast tests. Mean remifentanyl and naloxone-induced changes in (d) self-reported valence and (e) arousal for each movie clip. The clips are arranged according to the remifentanyl-induced change in valence ratings. N, negative clip; P, positive clip.⁸

During each infusion, participants saw 10 film clips in a random order and rated their experience of emotional valence (pleasure) and arousal. The stimulus material consisted of 30 brief film clips with varying affective valence (strong pleasure–strong displeasure) selected from a validated international database of well-known affective movies (<http://nemo.psp.ucl.ac.be/FilmStim/>).⁸ The film clips were grouped into three approximately 20-min sets (1179 s, 1182 s, 1183 s) with 10 clips in each, so that different videos with matched emotional content could be shown during each drug block. The average emotional valence of the three sets was matched based on the ratings in the database. In a clip-wise (F2) analysis, subject-wise valence and arousal responses were averaged for each individual clip. As the film clips were not available in the native language (Finnish) of the subjects, they were shown without sound.

Remifentanyl significantly increased the experience of pleasure, but not arousal, elicited by the film clips. This shift was seen across stimuli that were both unpleasant and pleasant. Naloxone shifted valence ratings for both negative and positive clips towards neutral, but had no effect on mean emotional valence or arousal ratings (Fig. 1). Analysis of clip-wise mean ratings also revealed that on average, remifentanyl caused a positive shift in valence (but not arousal) for nearly all clips. No differences in mean pleasure ratings between naloxone and saline conditions were found. The baseline personality or emotional status ratings were not significantly correlated with the variance or arousal evaluations. Four subjects reported nausea and five subjects reported sedation after remifentanyl administration.

Our results show that acute opioid administration shifts a range of emotional responses to the positive direction, amplifying positive and weakening negative feelings. Opioid antagonism shifted the valence ratings of both negative and positive clips towards neutral, suggesting that naloxone might overall diminish both positive and negative emotional experiences.

While these findings agree with a previous study, where remifentanyl increased the pleasantness ratings for neutral pictures,⁹ our results differ from data on orally administered opioids.^{4,5} The difference between remifentanyl, morphine, and oxycodone might be explained by the small oral doses (10–20 mg) and the route of administration. Oral administration of an opioid may be subject to inter-individual variation in absorption and distribution of the drug. The peak plasma concentration of oral oxycodone and morphine occurs at 1–2 h whereas with i.v. remifentanyl it is achieved in 1–3 min. Thus, the effects of oral opioids may be less predictable and sensitive than those of target-controlled i.v. opioid infusions.

It is important to understand the role of opioids in the modulation of emotional responses to sensory stimuli and also in mood after both acute and prolonged administration. Although small doses of acutely administered opioids cause euphoria, the effects in chronic opioid use can be different. In chronic opioid use, the brain reward system becomes altered, resulting in neuroadaptation, tolerance, and less responsiveness to natural reward. Consequently, emotional reactivity is blunted and the risk of depression increased.

Naloxone, like naltrexone, is a non-selective opioid receptor antagonist. Previously, opioid antagonism has been shown to cause no dampening of pleasure caused by emotional stimuli, or to reduce the pleasure of attractive faces, gambling rewards, or social bonding. These mixed results could be explained by the different doses of opioid antagonists used and the different emotional stimuli. As the dose of naloxone in

our study was smaller than that in some of the previous naloxone studies,^{3,10} the negative effects of naloxone on emotional responses to both pleasant and unpleasant stimuli did not reach statistical significance.

Together, these findings suggest that emotional responses to external stimuli are mediated by the opioid system. Short-term exogenous opioid administration increases the emotional valence of the stimuli, while emotional arousal remains unchanged. This may be one of the reasons behind the first opioid experiences developing to an opioid use disorder (e.g. after opioid use in the treatment of postoperative pain).

Authors' contributions

Designed the study and wrote the protocol: EK, LN, ML, ME, JJ, MS

Conducted the study: ML, JS, MS, JJ, TH, ME, EA

Contributed to the data analysis: ML, JS, MS, JJ, TH, TL, LN, EK

Wrote the first draft of the manuscript: TH

Contributed to and have approved the final manuscript: all authors

Declaration of interests

TH has served as continuing medical education (CME) speaker for Mundipharma and Roche. EK has served as advisory board member for Pierre Fabre, Gruenthal, and Orion Pharma. All other authors declare that they have no conflicts of interest.

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References

1. Leknes S, Tracey I. A common neurobiology for pain and pleasure. *Nature* 2008; **9**: 314–9
2. Nummenmaa L, Tuominen L. Opioid system and human emotions. *Br J Pharmacol* 2017; **175**: 2737–49
3. Eippert F, Bingel U, Schoell E, Yacubian J, Buchel C. Blockade of endogenous opioid neurotransmission enhances acquisition of conditioned fear in humans. *J Neurosci* 2008; **28**: 5465–72
4. Wardle MC, Fitzgerald DA, Angstadt M, Rabinak CA, de Wit H, Phan KL. Effects of oxycodone on brain responses to emotional images. *Psychopharmacology (Berl)* 2014; **231**: 4403–15
5. Loseth GE, Eikemo M, Isager P, et al. Morphine reduced perceived anger from neutral and implicit emotional expressions. *Psychoneuroendocrinology* 2018; **91**: 123–31
6. Wise RG, Williams P, Tracey I. Using fMRI to quantify the time dependence of remifentanyl analgesia in the human brain. *Neuropsychopharmacology* 2004; **29**: 626–35
7. Koppert W, Filitz J, Tröster A, et al. Activation of naloxone-sensitive and -insensitive inhibitory systems in a human pain model. *J Pain* 2005; **6**: 757–64
8. Schaefer A, Nils F, Sanchez X, Philippot P. Assessing the effectiveness of a large database of emotion-eliciting

- films: a new tool for emotion researchers. *Cogn Emot* 2010; **24**: 1153–72
9. Gospic K, Gunnarsson T, Fransson P, Ingvar M, Lindefors N, Petrovic P. Emotional perception modulated by an opioid and a cholecystokinin agonist. *Psychopharmacology (Berl)* 2008; **197**: 295–307
10. Petrovic P, Pleger B, Seymour B, et al. Blocking central opiate function modulates hedonic impact and anterior cingulate response to rewards and losses. *J Neurosci* 2008; **28**: 10509–16

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